What is NTRK?

NTRK stands for Neurotrophic tyrosine receptor kinase. Its function is to help the TRK proteins with cell signaling. Cells use signaling for many things; storing nutrients, creating energy, and reproduction are among them. Altered reproductive function can lead to the development of cancer in the body.

NTRK gene fusions may be found in some types of cancer, including cancers of the brain, head and neck, thyroid, soft tissue, lung, and colon.
A mutation (change) that occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow.

Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are an actionable biomarker for cancer therapy and can be found in over 25 different types of cancer, regardless of where they are located in the body.

- The TRK proteins are receptor kinases that help regulate cell signaling and function in healthy tissues.
- Rearrangements in the NTRK genes can result in two genes fusing together and producing altered TRK proteins, which can lead to uncontrolled growth of cancer cells.
- Similar to other cancer biomarkers, NTRK gene fusions are identified with biomarker tests, which can include next-generation sequencing (NGS), immunohistochemistry (IHC), DNA fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR).
- Biomarker testing for NTRK gene fusions is the only way to identify people who may be eligible for therapies that target these genomic alterations.

Recent advances in precision medicine mean that NTRK fusion-positive tumors may be appropriate for treatment with a targeted medicine regardless of the type of cancer or where it originated.

This is called a tumor-agnostic treatment approach.
First-generation TRK inhibitors, such as larotrectinib (Vitrakvi®) or entrectinib (Rozlytrek®), is associated with high response rates (>75%), regardless of tumour histology.

Health Canada has issued marketing authorization for the use of larotrectinib (Vitrakvi®) for the treatment of adult and pediatric patients with solid tumours that have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options. The marketing authorization was issued with conditions, pending the results of trials to verify its clinical benefit. A positive funding recommendation has been issued by CADTH for Vitrakvi® for the treatment of NTRK positive cancers.

Entrectinib (Rozlytrek®) is an oral medication, approved by Health Canada for the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours including brain metastases, that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options.

Despite durable disease control in many patients, advanced-stage NTRK fusion-positive cancers eventually become refractory to TRK inhibition. Fortunately, certain resistance mutations can be overcome by second-generation TRK inhibitors, including LOXO-195 and TPX-0005 that are being explored in clinical trials.